
This poster announced the "Imaging the Pancreatic Beta Cell Workshop" held in April 2013, which was co-sponsored by the NIDDK, JDRF, and the European Union. Shown on the poster is a human pancreatic islet, which contains many different cell types, including insulin-producing beta (β) cells (stained green) and glucagon producing alpha cells (stained red). In type 1 and type 2 diabetes, β cells are lost or cease secreting enough insulin to regulate a person's blood glucose levels. At the workshop, scientists discussed recent research progress and emerging opportunities in β cell imaging. The objective of this research is to develop imaging approaches that could be used to monitor the mass, function, and inflammation of naturally occurring or transplanted β cells in the body, in people with type 1 or type 2 diabetes, or in people who are at risk for these diseases. Imaging the β cell holds promise as a means to allow scientists to visualize the extent of pancreatic damage and, potentially, to see directly if a therapy is effective.

*Islet image provided by the laboratory of Dr. Alvin Powers, Vanderbilt University.*

# Diabetes, Endocrinology, and Metabolic Diseases

*NIDDK support of basic and clinical research in the areas of diabetes, endocrinology, and metabolic diseases spans a vast and diverse range of diseases and conditions, including diabetes, osteoporosis, cystic fibrosis, and obesity. Together, these diseases and conditions affect many millions of Americans and can profoundly decrease quality of life. Many of these diseases are complex—an interplay between genetic and environmental factors contributes to disease development.*

Diabetes is a debilitating disease that affects an estimated 25.8 million people in the United States—or 8.3 percent of the total population—and is the seventh leading cause of death.[1] Compared with people of similar age without the disease, diabetes doubles people's overall risk of death, as well as increases their risk of death from cardiovascular disease two- to four-fold. Diabetes is also the leading cause of kidney failure, nontraumatic lower limb amputations, and, in working-age adults, blindness.[1] In addition to these human costs, the estimated total financial cost for diabetes in the United States in 2012—including costs of medical care, disability, and premature death—was $245 billion.[2] Effective therapy can prevent or delay diabetic complications, but approximately one-quarter of Americans with diabetes are undiagnosed and therefore not receiving therapy.[1]

Diabetes is characterized by the body's inability to produce and/or respond appropriately to insulin, a hormone that is necessary for the body to absorb and use glucose (sugar) as a cellular fuel. These defects result in persistent elevation of blood glucose levels and other metabolic abnormalities, which in turn lead to the development of disease complications. The most common forms of diabetes are type 1 diabetes, in which the body loses its ability to produce insulin, and type 2 diabetes, in which the body becomes resistant to insulin signaling, with subsequent impaired insulin production. In addition, a significant proportion of pregnant women each year are diagnosed with gestational diabetes, a form of diabetes that is similar to type 2 diabetes but unique to pregnancy. Untreated, any form of diabetes during pregnancy increases the risk of serious complications for the mother and baby before, during, and after delivery.

Type 1 diabetes, formerly known as juvenile diabetes, affects approximately five percent of adults and the majority of children and youth with diagnosed diabetes.[1] It most often develops during childhood, but may appear at any age. Type 1 diabetes is an autoimmune disease in which the immune system launches a misguided attack and destroys the insulin-producing beta (β) cells of the pancreas. If left untreated, type 1 diabetes results in death from starvation: without insulin, glucose is not transported from the bloodstream into the body's cells, where it is needed. Thus, patients require lifelong insulin administration—in the form of multiple daily injections or via an insulin pump—in order to regulate their blood glucose levels. The NIDDK's landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated that keeping blood glucose levels as near to normal as safely possible reduced the risk of eye, kidney, nerve, and heart complications associated

[1] *2011 National Diabetes Fact Sheet. Centers for Disease Control and Prevention. Atlanta, GA.*

[2] *American Diabetes Association. Diabetes Care 36: 1033-1046, 2013.*

with type 1 diabetes. Thirty years after the launch of the DCCT in 1983, the DCCT and EDIC studies continue to provide important information about type 1 diabetes and its complications. However, despite vigilance in disease management, with frequent finger sticks to test blood glucose levels and the administration of insulin, it is still impossible for patients to control blood glucose levels to levels achieved by functional β cells. Thus, researchers are actively seeking new methods to improve blood glucose monitoring and insulin delivery, including technology to link them in an "artificial pancreas," as well as working to develop β cell replacement therapies to cure type 1 diabetes.

Type 2 diabetes is the most common form of the disease, accounting for about 90 to 95 percent of diagnosed diabetes cases in U.S. adults.[1] Type 2 diabetes is associated with several factors, including older age and a family history of the disease. It is also strongly associated with obesity; more than 80 percent of adults with diabetes are overweight or obese.[3] Type 2 diabetes occurs at higher rates among minority groups, including African Americans, Hispanic and Latino Americans, American Indians, and Native Hawaiians and Pacific Islanders.[1] Gestational diabetes is also a risk factor: women who have had gestational diabetes have a 35 to 60 percent chance of developing diabetes—mostly type 2 diabetes—in the next 10 to 20 years.[1]

In people with type 2 diabetes, cells in muscle, fat, and liver tissue do not properly respond to insulin. As a result, the pancreas initially produces more insulin to compensate. Gradually, however, the pancreatic β cells lose their ability to secrete enough insulin to restore balance, and the timing of insulin secretion becomes abnormal, causing blood glucose levels to rise. Treatment approaches for controlling glucose levels include diet, exercise, and oral and injected medications, with insulin often required as the disease progresses. There are also an estimated 79 million adults in the United States who have a condition called "prediabetes," in which blood glucose levels are higher than normal, but not as high as in diabetes.[1] This population is at high risk of developing diabetes. Fortunately, the NIDDK-supported Diabetes Prevention Program (DPP) clinical trial has shown that people with prediabetes can dramatically reduce their risk of developing type 2 diabetes with diet and exercise changes designed to achieve a seven percent reduction in body weight. Moreover, follow-up research has shown that this benefit of reduced diabetes risk can persist for at least 10 years.

Type 2 diabetes was previously called "adult-onset" diabetes because it is predominantly diagnosed in older individuals. However, this form of diabetes is increasingly being diagnosed in children and adolescents, and it disproportionately affects minority youth. Believed to be related to increasing rates of pediatric obesity, this is an alarming trend for many reasons. For example, the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial showed that the disease may be more aggressive and difficult to treat in youth compared to adults. This is worrisome because the onset and severity of disease complications correlate with both the duration of diabetes and control of blood glucose levels; thus, those with early disease onset are at greater risk with respect to complications than those who develop the disease later in life. The TODAY study continues to provide valuable information on type 2 diabetes in youth, including data on poor risk factor control and emerging complications among study participants, highlighting the urgent need for further research toward effectively preventing and treating type 2 diabetes in youth. In addition, increasing rates of type 2 diabetes in girls may lead to more women who enter pregnancy with diabetes, and maternal diabetes during pregnancy—either onset of type 2 diabetes before pregnancy or the development of gestational diabetes during pregnancy—confers an increased risk of type 2 diabetes in offspring. Thus, the rising rates of diabetes and prediabetes in young women could lead to a cycle of ever-growing rates of diabetes. Therefore, the advent of type 2 diabetes in youth has the potential to worsen the enormous health burden that diabetes already places on the United States.

The NIDDK is supporting research to better understand metabolism and the mechanisms that lead to the

[3] *Eberhardt MS, et al. MMWR 53: 1066-1068, 2004.*

development and progression of diabetes and the many other endocrine and metabolic diseases within the NIDDK's mission; such research will ultimately spur the design of potential new intervention strategies. In parallel, based on knowledge from past scientific research investments, the NIDDK is vigorously pursuing studies of prevention and treatment approaches for these diseases.

## BETA CELLS AND DIABETES

**New Class of Genes Involved in Beta Cell Maturation and Diabetes:** Researchers have identified a new class of genes that plays a role in maturation of pancreatic insulin-producing beta (β) cells and may be involved in diabetes. RNA has been known historically as the intermediate between DNA and proteins: DNA is decoded into RNA, which in turn is translated into protein. However, recent research has discovered the presence of numerous RNA molecules that are encoded from DNA but not translated into proteins. A subset of these RNAs is called "long non-coding RNAs" (lncRNAs), and their function is largely unknown, although research suggests that some may be involved in regulating whether genes are turned on or off (gene expression). While many protein-coding RNAs are often present in several different cell types, lncRNAs are often found only in a single cell type. This observation suggests that lncRNAs may regulate cell-specific tasks, and potentially makes them attractive targets for therapy to affect one cell type.

Because β cells are central to the development of both type 1 and type 2 diabetes, researchers sought to identify lncRNAs that were expressed in human pancreatic islets, which are primarily composed of β cells. They identified over 1,100 lncRNAs expressed in islets, with about half of them expressed in islets only. They next looked at a subset of lncRNAs, to determine when they were expressed during β cell development. The lncRNAs were not present in early progenitor cells, but were active in mature islets, suggesting that they may play a role in promoting β cell maturation. Additional experiments suggested that lncRNAs may function by controlling the expression of islet-specific genes. These findings are important because a major goal of diabetes research is to identify strategies to turn progenitor cells into mature β cells, and this research has identified a class of molecules that may be involved in this process and/or could be markers of mature β cells.

The researchers next examined whether the lncRNAs may play a role in type 2 diabetes. They discovered a small number of lncRNAs that were abnormally expressed in human islets from people with type 2 diabetes, and others that were located near genetic regions previously shown to be associated with susceptibility to type 2 diabetes, suggesting that lncRNA abnormalities may explain part of the genetic susceptibility to type 2 diabetes. This research has therefore identified a new class of genes that are expressed in islets, promote maturation of β cells, and may play a role in type 2 diabetes. It also opens up new avenues for studying and potentially promoting β cell maturation, and for examining the underlying genetic causes of diabetes toward identifying new targets for therapy.

*Morán I, Akerman I, van de Bunt M, et al. Human β cell transcriptome analysis uncovers lncRNAs that are tissue-specific, dynamically regulated, and abnormally expressed in type 2 diabetes. Cell Metab 16: 435-448, 2012.*

**Protein on Surface of Beta Cells Is Possible Type 2 Diabetes Drug Target:** Researchers discovered that a protein found on the surface of insulin-producing beta (β) cells in the pancreas may be an attractive drug target to prevent or treat type 2 diabetes. In type 2 diabetes, β cells do not release enough insulin to maintain healthy blood glucose levels. This defect is due to impairments in β cell function combined with reduced numbers of β cells (referred to as β cell mass). Scientists examined whether turning on (activating) a protein—called a $G_q$-coupled receptor—found on the surface of β cells would have an effect on β cell mass or function in mice. A related protein, a $G_s$-coupled receptor, is already the target of type 2 diabetes drugs in humans, so the researchers wanted to determine if the $G_q$-coupled receptor could also be a potential drug target. Like the $G_s$ form of the protein, the $G_q$ form is found on

many different cell types. Thus, to study the $G_q$ form in β cells only, they used an experimental mouse model they had previously generated, which made a "designer" $G_q$-coupled receptor specifically in β cells. The designer receptor could be activated by giving the animals a compound that was otherwise biologically inert.

The scientists discovered that chronically activating the designer $G_q$-coupled receptor with the compound resulted in a robust increase in the animals' β cell mass and function. This was associated with increased expression (turning on) of several genes known to be involved in promoting β cell development or maintaining normal β cell function. Activating the receptor prevented the animals from developing diabetes induced by a toxin that destroys a large percentage of β cells. It also prevented the metabolic defects seen when mice eat a high-fat diet. These results suggest that $G_q$-coupled receptors play an important role in regulating β cell function and blood glucose levels in mice. If they play a similar role in humans, they would be attractive targets for drug development to combat type 2 diabetes. Because the receptors are found on other cell types, therapeutic approaches would need to activate receptors found on β cells specifically so as to minimize side effects.

*Jain S, Ruiz de Azua I, Lu H, White MF, Guettier JM, and Wess J. Chronic activation of a designer $G_q$-coupled receptor improves β cell function. J Clin Invest 123: 1750-1762, 2013.*

**Newly Discovered Hormone Increases Beta Cell Proliferation in Mice:** Researchers have discovered a new hormone, called betatrophin, that promotes pancreatic beta (β) cell proliferation and improves glucose control in mice. Scientists hope the finding may lead to new ways to prevent or slow the progression of diabetes in humans. β cells, which produce the hormone insulin, are destroyed by the immune system in people with type 1 diabetes and may not function normally in people with type 2 diabetes. Identifying ways to replace lost β cells and restore the body's insulin-producing capacity would benefit people with type 1 or type 2 diabetes and is a major research goal. Previous research found that blocking insulin signaling in tissues such as the liver resulted in β cell proliferation and increased insulin secretion. To determine what causes this effect, and to provide clues to what cellular factors may regulate β cell proliferation, researchers treated mice with a molecule that blocked insulin signaling and then studied what genes were turned on as β cells proliferated. They identified a gene that was turned on in the liver and fat of treated mice. The gene was found to encode a protein, which they named betatrophin. The researchers discovered that the protein is secreted by the liver and fat, and travels through the bloodstream. Increasing the amount of betatrophin produced in mice tripled the mass of their pancreatic β cells in just eight days, doubled insulin production, and led to a lower fasting glucose level and improved glucose tolerance compared to control mice. Humans have a very similar gene, though whether or not human betatrophin plays a similar role as mouse betatrophin is currently under investigation. Research to understand what proteins betatrophin interacts with, how betatrophin stimulates β cell proliferation, and what betatrophin's other functions might be is still ongoing and could possibly lead to new therapies.

*Yi P, Park JS, and Melton DA. Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell 153: 747-758, 2013.*

## ADVANCING TECHNOLOGY IN DIABETES MANAGEMENT

**Smartphone Technology Advances Progress Toward the Development of an Artificial Pancreas for People with Type 1 Diabetes:** Researchers used smartphone technology to move a step closer toward developing an artificial pancreas. An artificial pancreas, or a "closed-loop system," is technology in which a computer calculates insulin dose based on glucose levels and delivers insulin automatically through an insulin pump with minimal human input. Such technology holds great promise to help people safely achieve recommended levels of blood glucose control, as well as to alleviate an enormous amount of patient burden associated with current self-management strategies. Significant progress toward developing an artificial pancreas has been achieved in recent years, with researchers testing closed-loop systems in people in hospital settings using

laptop computers, which limits mobility. To realize the promise of this technology, patients need a portable and wearable system so that they can carry out activities of daily life.

In new research, scientists tested whether smart phone technology could replace laptops to control a closed-loop system. They tested their new technology, called the Diabetes Assistant (DiAs), in 20 people with type 1 diabetes at four sites in the United States and Europe. DiAs (on a smartphone) communicated wirelessly with a communication box, which in turn signaled wirelessly to a continuous glucose monitor (which measures blood glucose levels) and an insulin pump. After participants were given a brief orientation about how to use DiAs, they used the system on their own. Participants stayed in real world settings, such as hotels, and ate whatever they wanted; to ensure that they were safe at all times, they were closely monitored by study personnel.

The study found that the artificial pancreas system had proper system communication 98 percent of the time, which was higher than the goal of 80 percent in this study. The researchers concluded that smartphone technology could be used to run a closed-loop system, and that DiAs is a promising platform for future study. The technology has already advanced since this study was conducted, and the intermediate device (communication box) is being phased out. This research is an important step forward toward developing a portable, usable, and safe artificial pancreas system, and sets the stage for future clinical trials.

*Kovatchev BP, Renard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 36: 1851-1858, 2013.*

## CARDIOVASCULAR DISEASE RISK IN YOUTH WITH TYPE 1 DIABETES

**Increased Understanding of Cardiovascular Disease Risk Factors in Youth with Type 1 Diabetes:** Two studies of cardiovascular disease (CVD) risk factors in youth with type 1 diabetes provide new information about progression of CVD in this population, and about potential prevention strategies. Type 1 diabetes, like type 2 diabetes, is associated with an array of serious, long-term complications, including CVD. People with diabetes have a greatly increased risk for CVD, CVD occurs earlier in people with diabetes than in people without diabetes, and CVD is the leading cause of mortality in people with diabetes. Youth with type 1 diabetes will endure a higher lifetime burden of diabetes than adults and, therefore, a higher burden of complications, including CVD. It is not known, however, whether CVD in youth with type 1 diabetes has similar risk factors and/or the same progression to advanced disease as in adults. By studying the natural history of CVD and examining CVD risk factors in youth with type 1 diabetes, scientists from the SEARCH for Diabetes in Youth CVD Study gained insights that could lead to strategies to prevent or treat CVD in this population.

In the first study, SEARCH scientists examined heart rate variability in youth with type 1 diabetes. The autonomic nervous system regulates heart rate, enabling changes in heart rate in response to activity/stress and rest. Reduced heart rate variability is a sign of cardiac autonomic neuropathy, a complication of diabetes that increases the risk of mortality. The researchers found that youth with type 1 diabetes have reduced overall heart rate variability, particularly youth with suboptimal blood glucose control, compared to youth without type 1 diabetes. In the other study, SEARCH scientists examined the "carotid intima-media thickness" (IMT) of youth with type 1 diabetes. IMT is a measure of the thickness of the arterial wall of the carotid artery, which supplies the head and neck with oxygenated blood. A thickening of the arterial walls can indicate the presence of atherosclerosis. In adults, type 1 diabetes leads to an increase in carotid IMT. In this study, the researchers found that youth with the disease also had increased IMT and that this association may be attributable to poor blood glucose control, compared to youth without type 1 diabetes. Therefore, both heart rate variability and IMT are altered in youth with type 1 diabetes, indicating that this population shows signs of CVD risk early in the course of the disease.

The NIDDK's Diabetes Control and Complications Trial (DCCT) and its follow-up study, Epidemiology of Diabetes Interventions and Complications, found that adults with type 1 diabetes who had intensive blood glucose control during the DCCT had about half the rate of CVD events compared to those who received conventional treatment. The SEARCH CVD study has provided novel data about CVD and its risk factors in youth with type 1 diabetes, and the findings continue to suggest the importance of good blood glucose control to prevent CVD in people with the disease.

*Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care 36: 157-162, 2013.*

*Urbina EM, Dabelea D, D'Agostino RB Jr, et al. Effect of type 1 diabetes on carotid structure and function in adolescents and young adults: the SEARCH CVD study. Diabetes Care 36: 2597-2599, 2013.*

## UNDERSTANDING THE MECHANISM OF A DRUG USED TO TREAT TYPE 2 DIABETES

**New Mechanism Proposed for Glucose-lowering Effect of Metformin, a Drug for Type 2 Diabetes:** A new report may explain how the diabetes drug metformin exerts its effects, providing a potential target for development of new therapeutics. The liver plays an important role in blood glucose (sugar) levels by sending glucose into the bloodstream when levels start to drop between meals. Liver glucose output during fasting is triggered by glucagon, a hormone secreted by the pancreas that works in opposition to another hormone, insulin, which the pancreas secretes when blood glucose levels are high (after meals). In people with type 2 diabetes, not only does the body become resistant to the glucose-lowering effect of insulin, but it also produces glucagon inappropriately. As a result, glucose enters the bloodstream from the liver when it is not needed, contributing to high blood glucose levels. The most commonly prescribed oral drug for treatment of type 2 diabetes, metformin, helps control blood glucose levels by reducing the amount of glucose coming from the liver. How it is able to do this has been unclear. Metformin treatment causes an increase in the levels of a molecule called AMP. AMP activates an enzyme called AMPK, and the activated AMPK was thought to reduce liver glucose production, accounting for metformin's effects. Now, working in mouse liver cells and mouse models, researchers have uncovered evidence strongly suggesting that metformin interferes with glucagon-induced glucose output by disrupting the initial steps of glucagon signaling in liver cells. In particular, their data suggest that the metformin-induced rise in AMP inhibits glucagon's activation of an enzyme called adenylate cyclase, the first step in the molecular signal for glucose production inside liver cells. If this theory is borne out, it paves the way to developing potential new drug treatments for type 2 diabetes that specifically target this enzyme. These findings also reinforce the importance of glucagon and finding ways to minimize its abnormal activity in type 2 diabetes.

*Miller RA, Chu Q, Xie J, Foretz M, Viollet B, and Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 494: 256-260, 2013.*

## ADVANCES IN CYSTIC FIBROSIS TESTING AND TREATMENT

**An Important Proof of Principle for the "Combination Therapy" Approach to Treating the Most Common Cystic Fibrosis Mutation:** New research has shown that it may one day be possible to treat people with cystic fibrosis (CF) using a combination of medicines that work cooperatively to stabilize an aberrant form of CFTR, the protein that is defective in CF. Among people with CF, the most common genetic mutation causing the disease is designated *cftr-ΔF508*. The U.S. Food and Drug Administration recently approved a "small molecule corrector" drug that alleviates CF when it is caused by a less common *CFTR* mutation (found in roughly five percent of CF patients), allowing patients with the rarer mutation to lead their lives with far fewer symptoms of the disease. However, researchers have not yet been successful in taking a similar approach

to find small molecule correctors for the *cftr-ΔF508* mutation. While several candidate small molecule drugs have been found to improve stability of the cftr-ΔF508 protein in the laboratory, clinical trials are still under way with people with this mutation, so their therapeutic value is not yet known. Previous NIDDK-supported research identified a possible explanation: *ΔF508* destabilizes multiple "domains" of the protein (distinct sections of the protein which fulfill specific biological roles). In particular, *ΔF508* disrupts two "nucleotide binding domains" (designated NBD1 and NBD2), as well as the interaction of NBD1 with critical regions that connect parts of the protein that are inside the cell with a portion that is outside the cell, termed "membrane spanning" domains. The new study characterizes the existing candidate drugs in terms of which domain they stabilize, effectively defining three classes of corrector compounds. Existing correctors stabilize the interaction of NBD1 with the first and second membrane spanning domains (class I) or stabilize NBD2 (class II). Also necessary is stabilization of NBD1 itself (class III), achieved in this study by using the chemical glycerol or other "chemical chaperones." In a key test on human lung cells grown in the laboratory that harbored the *cftr-ΔF508* mutation, they found that using only one or two classes of correctors resulted in very little CFTR activity; but combined treatment with all three classes of correctors achieved almost normal levels of CFTR function. The chemical chaperones that serve as class III correctors in this study are unlikely themselves to be medicinally useful. For example, because glycerol is a naturally occurring compound that is freely metabolized by the body, it would not reach target tissues in sufficient concentration to function as a therapeutic agent. However, these results strongly suggest a potential benefit for focusing efforts on finding compounds that stabilize the NBD1 domain of the cftr-ΔF508 protein. The research suggests that if a compound that can do so proves safe in combination with existing class I and class II correctors, the approach may greatly improve treatment for the majority of people with CF.

*Okiyoneda T, Veit G, Dekkers JF, et al. Mechanism-based corrector combination restores ΔF508-CFTR folding and function. Nat Chem Biol 9: 444-454, 2013.*

**Improving Genetic Testing for Cystic Fibrosis:**
New research has greatly expanded knowledge of the specific mutations capable of causing cystic fibrosis (CF). Previous landmark research established that CF is caused by mutations in a gene, *CFTR*, encoding a critical channel protein that enables the movement of chloride in and out of cells. Everyone has two copies of *CFTR*, one inherited from each parent. Those with CF have mutations that disrupt the function of both of their *CFTR* copies. People with a single CF-causing mutation are often unaware of it, because their one functioning *CFTR* copy is enough to keep them healthy. Therefore, when considering having children, couples with CF in one of their families will often pursue genetic testing and counseling to determine the likelihood that one of their children will have the disease. If one copy of a known CF-causing mutation is found through either prenatal or newborn screening, it may be uncertain whether a variant in the baby's other copy of *CFTR* would lead to the development of CF. However, although research has identified over 2,000 variations in the *CFTR* gene, only 23 of these were previously shown to be capable of causing CF. While most of the other known variants are likely to be harmless, sometimes genetic testing reveals a variant of unknown significance in potential parents, so genetic counselors cannot tell them with confidence what their odds are of conceiving a child with CF.

To better understand which *CFTR* mutations pose a risk of causing CF, researchers examined genetic records of almost 40,000 people diagnosed with CF—estimated to be more than half of the world population with the disease—for whom clinical measurements of CFTR chloride channel function had been recorded. Confining their analysis to 159 variants found in at least 0.01 percent (one in 10,000) of people with CF in the database they had assembled, the researchers tested how these *CFTR* mutations affect chloride transport when introduced into cells grown in the laboratory, and compared the results of those tests to clinical measurements of CF from their database. As a result, they were able to unambiguously identify 104 specific CF-causing *CFTR* variants in addition to those already known, for a total of 127. For the remaining 32 variants, the clinical data appeared

inconsistent with CF, or the laboratory function tests indicated a variant that should function reasonably well, or both. This may at first seem surprising, since a person with CF should not have a fully functional copy of *CFTR*, but in some cases a benign change may lie alongside a second *CFTR* mutation that does cause disease. Other variants may ordinarily be harmless, but might have the capacity to promote CF symptoms in people with other (unknown) genetic or environmental risk factors. Because men carrying a CF-causing mutation must also have one normally functioning copy of the *CFTR* gene in order to be fertile, the researchers furthered their analysis by examining fathers of CF patients to see if any of them had one of the remaining 32 variants in one copy of their *CFTR* genes, along with a known disease-causing variant in the other. Ten of the 32 variants were found to occur more frequently among the healthy fathers than among people with CF, indicating they do not normally cause disease, even when the other *CFTR* copy contains a disease-causing mutation. Two more were ruled out as disease-causing for other reasons. The remaining 20 variants were not more common among the healthy fathers and could not be ruled out in other ways, so it remains possible that they contribute to disease. As a result of these findings, CF genetic testing will be much more comprehensive, and provide greater certainty to parents concerned about their children's chance of having the disease. Moreover, the laboratory models of the different *CFTR* variants created through this research may promote better understanding of the physiology of the CFTR chloride channel, and may one day lead to improvements in CF patient care.

*Sosnay PR, Siklosi KR, Van Goor F, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet 45: 1160-1167, 2013.*

## INSIGHTS ON RARE METABOLIC DISORDERS

**Discoveries May Improve Treatment of Mucopolysaccharidosis:** Two recent studies in animal models have reported encouraging findings in the quest to improve treatment for people with mucopolysaccharidosis. In this group of genetic diseases, the lack of any one of several enzymes used by cells throughout the body to digest and recycle substances they no longer need leads to accumulation of one or more cellular waste products. These undigested substances are stored in the cells, where they cause serious problems that can include weakness, severe pain, brittle bones, intellectual disability, clouding of the cornea of the eye, organ failure, and death. Periodic infusions of purified replacement enzymes, which cells can absorb and utilize, have been developed as therapies for three types of mucopolysaccharidosis: type I, type II, and type VI (MPS I, MPS II, and MPS VI).

While enzyme replacement greatly alleviates many disease symptoms, lengthening and improving quality of life, such therapies are not cures. A major limitation of the approach has been that the replacement enzymes do not reach some of the tissues where they are needed, including bone, cartilage, and brain, which is separated from the blood by the so-called blood-brain barrier. Therefore, the enzyme therapies provide little or no relief from cognitive and other neurological disease manifestations.

Researchers recently identified a potential solution to this problem, and reported encouraging results in experiments with mice lacking the same enzyme as people with MPS I. The scientists noted that the blood-brain barrier is crossed by a small number of other proteins, and identified the portion of one of these proteins that allows it to move from blood into the brain. They then attached the MPS I replacement enzyme to that key part of the blood-brain barrier-crossing protein and showed that the resulting hybrid protein reached brain cells of MPS I mice, where it dramatically reduced levels of accumulated cellular waste.

Research from a different group has identified another potential therapeutic improvement. Researchers have found that bone and cartilage problems in animal models of various mucopolysaccharidoses are similar to those in people with these diseases. They also found that these problems result, at least in part,

from inflammation triggered by accumulated cellular waste products. These observations suggest that an anti-inflammatory medication might lessen some symptoms in bone and other tissues inaccessible to replacement enzymes or when enzyme replacement therapy is not available. The researchers, therefore, tested pentosan polysulfate, a medication known to reduce inflammation and promote cartilage growth that is approved by the U.S. Food and Drug Administration for treatment of a painful urologic condition, interstitial cystitis/painful bladder syndrome. When the drug was given to rats with MPS VI, the researchers observed significant improvements in bone, cartilage, and tooth structure, as well as some other symptoms. The treated rats were also more mobile and behaved more normally than did untreated control animals, even though cellular waste products continued to accumulate in their bodies.

Further research will be necessary to determine if modifying replacement enzymes to allow their transport across the blood-brain barrier or treatment with pentosan polysulfate—alone or in conjunction with other therapies—may be safe and therapeutically beneficial treatment approaches for lysosomal storage disorders. If so, they may one day allow people with these diseases to lead longer, healthier lives.

*Wang D, El-Amouri SS, Dai M, et al. Engineering a lysosomal enzyme with a derivative of receptor-binding domain of apoE enables delivery across the blood-brain barrier. Proc Natl Acad Sci USA 110: 2999-3004, 2013.*

*Schuchman EH, Ge Y, Lai A, et al. Pentosan polysulfate: a novel therapy for the mucopolysaccharidoses. PLoS One 8: e54459, 2013.*

# *The Course of Type 2 Diabetes and Complication Onset in Youth Today*

Four new analyses of data from the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial have revealed important information about the challenges of controlling type 2 diabetes progression and preventing its complications in young people. Although type 2 diabetes is most commonly diagnosed in people over the age of 40, an increase in childhood obesity and other factors has led to a significant rise in cases in people under 20 years of age. Prior to this study, it was unknown whether treatments developed for adults would work well for younger patients. TODAY tested how well three treatment approaches controlled blood glucose levels in ethnically and racially diverse youth ages 10 to 17 who were overweight or obese and had been diagnosed with type 2 diabetes no more than two years before enrollment in the study. All participants received metformin, the first-line drug of choice among adults with type 2 diabetes, and currently the only oral medication approved for use in children. Participants were randomly assigned to receive metformin alone; metformin plus another diabetes drug, rosiglitazone; or metformin plus a program of intensive lifestyle changes aimed at helping participants lose weight and increase physical activity. Unfortunately, metformin alone failed to maintain acceptable, long-term, blood glucose control in most participants over an average follow-up of 46 months—a much higher failure rate than expected—and the addition of the lifestyle intervention provided only a modest improvement that was not statistically significant. Although blood glucose levels remained healthier, on average, in participants who received both metformin and rosiglitazone than in the other groups, the two-drug combination still failed 38.6 percent of the time over the course of the study. Importantly, after the trial began, the U.S. Food and Drug Administration (FDA) restricted use of rosiglitazone because of studies linking the medicine to a higher risk of heart attacks and stroke in adults. Although the FDA recently lifted restrictions on use of rosiglitazone in adults, the drug remains unapproved for use in children.

Since publishing their initial results in 2012, TODAY researchers have examined the data to glean as much as possible about the way the different study treatments affected the participants' metabolic function, as well as their progression toward some of the serious complications of the disease. The cells of people developing type 2 diabetes do not absorb as much glucose as they should in response to insulin. At first, the pancreas compensates by producing more insulin, but when the organ can no longer keep up with demand, diabetes results. In most adults with type 2 diabetes, the pancreas gradually loses the capacity to produce insulin as the disease progresses, so supplementary insulin often becomes required. To better understand the way the disease progressed in youth in the three TODAY treatment groups, study scientists analyzed changes in participants' insulin resistance and capacity for pancreatic insulin production over the course of the trial. They found that average insulin sensitivity gradually fell for the metformin and metformin plus lifestyle groups, while for the metformin plus rosiglitazone group it improved significantly in the first six months of the trial, but later gradually fell back to initial levels.

Thus, at the end of the trial, average insulin sensitivity among those youth getting both medicines was about where it began, but it had worsened among those getting just metformin or metformin plus lifestyle. In contrast, insulin-production capacity fell similarly in all three groups. Importantly, TODAY scientists found that in all of the treatment groups, the participants with the poorest blood glucose control and insulin production at the beginning of the trial were the ones most likely to have higher than recommended blood glucose levels before the study ended. This points to the importance of beginning treatment for pediatric type 2 diabetes before significant loss of insulin production capacity or deterioration of blood glucose control occurs.

One of the major concerns about the increasing frequency with which type 2 diabetes is appearing in

young people is that data from studies in adults show that the onset and severity of diabetes complications correlate with the duration of the disease. Thus, there is great concern that having diabetes for the vast majority of their lives may leave these young people vulnerable to particularly early and severe disease complications.

TODAY researchers, therefore, examined participants for early signs of retinopathy, a diabetes complication of the eye that is the most common cause of adult-onset blindness. Study scientists photographed a majority of participants' retinas during the last year of the study and found that retinopathy was beginning to develop in almost 14 percent of those participants. Among the TODAY participants, increasing time since initial diagnosis of diabetes, greater age, and poorer blood glucose control were all associated with a greater likelihood of retinopathy, reinforcing the importance of early treatment of type 2 diabetes. At multiple stages during the trial, TODAY participants were also tested for key complication risk factors and early signs of kidney and heart complications. Thus, for example, TODAY researchers identified hypertension (high blood pressure)—a major risk factor for both heart attack and kidney disease, both common complications of diabetes—in more than 11 percent of participants when the study began, and almost 34 percent by the end of the study, an average of less than five years after developing diabetes. Boys were more likely than girls to have hypertension or develop it over the course of the trial. The more obese participants were, the more likely they were to have or develop high blood pressure, as well. These findings parallel results in adolescents who do not have diabetes, among whom obesity and male sex are risk factors for developing hypertension.

The researchers also looked for an early sign of kidney disease, the presence of a protein called albumin in urine. More than six percent of TODAY participants had elevated urine albumin when the study began, and more than 16 percent did when it ended; elevated urine albumin was most likely to occur in participants whose blood glucose was more poorly controlled. Two major risk factors for heart disease, dyslipidemia (the elevation of unhealthy blood fats and/or lowering of healthy blood fat levels) and signs of chronic inflammation, were also found to be present at concerning levels when the study began, and at increasing rates as it progressed. In general, none of the treatment approaches were clearly superior to the others at preventing the development of diabetes complications or their risk factors in the TODAY participants, underscoring the importance of further research to identify better ways to prevent, treat, or cure type 2 diabetes in the young.

*The TODAY Study Group. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. Diabetes Care 36: 1749-1757, 2013.*

*The TODAY Study Group. Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Care 36: 1772-1774, 2013.*

*The TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 36: 1735-1741, 2013.*

*The TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 36: 1758-1764, 2013.*

# *Collaborative Efforts Key to Catalyzing Creation of an Artificial Pancreas*

On April 9 and 10, 2013, dozens of scientists, engineers, and clinicians from North America, Europe, and the Middle East gathered on the NIH campus with the goal of improving the health and quality of life of people with diabetes. They were participants in the "Workshop on Innovation Towards an Artificial Pancreas," a forum on research and opportunities to accelerate the development and delivery of a promising technological approach to treatment and management of diabetes: a wearable, automated artificial pancreas. Organized by the NIDDK, the lead NIH Institute for artificial pancreas research; the U.S. Food and Drug Administration (FDA), the federal agency regulating medical devices; and the leading health advocacy group for people with type 1 diabetes, JDRF, this workshop represented just one of the latest in a continuing series of collaborative efforts that are helping to make the artificial pancreas a reality.

**Why an Artificial Pancreas?**

Both type 1 and type 2 diabetes cause the levels of glucose, or sugar, in the blood to rise above a normal, healthy range. When blood glucose levels are not well controlled, a person with diabetes is at much greater risk for developing devastating health complications, including blindness, kidney disease and kidney failure, nerve problems, and cardiovascular disease. These complications exact a heavy toll on both individuals and the health care system in terms of health and health care costs. Thus, finding ways to help people with diabetes optimize control of their blood glucose levels is a critical goal for research on diabetes treatment and management.

For people with type 1 diabetes, controlling blood glucose levels is especially challenging. Type 1 diabetes destroys the insulin-producing beta (β) cells of the pancreas. Without β cells, the pancreas is unable to sense rising glucose levels and respond with secretion of insulin, the hormone that enables the body to absorb glucose—the main source of energy derived from digestion of food—from the bloodstream. To try and keep blood glucose levels within a healthy range, people with type 1 diabetes must measure glucose levels multiple times daily and, based on complex calculations, administer insulin via injection or a pump. While recent advances in technology such as continuous glucose monitors (CGMs) and "smart" insulin pumps that can help calculate insulin doses have helped many patients, recapitulating the dynamic control of blood glucose levels imposed by the β cells of the pancreas is still impossible with current methods. Also, whereas a healthy pancreas has biological safeguards to help prevent blood glucose from dropping too low as well as rising too high, insulin therapy brings with it the risk of potentially life-threatening episodes of low blood glucose, or hypoglycemia, especially at night. Thus, researchers have been working intensively to advance technology that can replace the exquisite control of blood glucose by the pancreas, hoping to achieve an "artificial pancreas" that automatically closes the loop between glucose sensing and delivery of appropriate amounts of insulin, while also preventing hypoglycemia and imposing minimal burden on the user.

**Essential components of an artificial pancreas are:**

- A glucose-sensing component (sensor) that measures blood glucose levels and sends information to a computer;
- An insulin delivery device, such as an insulin pump; and
- A computer that calculates the amount of insulin needed and thereby "closes the loop" between glucose sensing and insulin delivery.

**Working Together To Advance the Field**

The design of any system capable of achieving what is expected of an artificial pancreas is complex, and raises novel scientific, clinical, and regulatory challenges. Thus, the NIDDK is working with the FDA and JDRF to help overcome these challenges so that safe and effective artificial pancreas systems can be developed and moved swiftly to market. For example, following a joint workshop on the artificial pancreas organized by the NIDDK, the FDA, and JDRF in 2005, the FDA in 2006 identified "Accelerating the Availability of the Artificial Pancreas" as one of its "critical path" initiatives—FDA's strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. Then, in 2007, the FDA partnered with the NIDDK and other NIH Institutes to develop a working group of federal scientists, clinicians, and regulatory experts who would work together and with stakeholders, such as JDRF, academic researchers, and industry, to find ways to accelerate and optimize research and development efforts toward an artificial pancreas. This Interagency Artificial Pancreas Working Group meets regularly to discuss research and regulatory issues surrounding this new technology, and has been instrumental in promoting the field, including contributing to the development and release of the FDA comprehensive guidance for artificial pancreas systems in November 2012. This guidance is helping researchers in academia and industry identify steps they need to take in the development of their artificial pancreas systems before applying to the FDA for permission to test device safety and effectiveness in people or to market their systems. Also, the April 2013 artificial pancreas workshop was the fourth such collaborative workshop organized by the NIDDK, the FDA, and JDRF in less than a decade to stimulate discussion of the current state of the art in artificial pancreas technology, technical difficulties and possible solutions, safety issues, and next steps.

While the NIH has supported research in this field for over two decades, in the last several years the NIDDK has intensified its artificial pancreas research program as well as its collaborations with other NIH Institutes and JDRF. For example, since 2008, the NIDDK, in partnership with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), has released four funding opportunity announcements to solicit innovative research on artificial pancreas systems by small businesses. The NIDDK has also participated in the NICHD-led Diabetes Research in Children Network, or DirecNet, which has investigated the use of technological advances in the management of type 1 diabetes in children and adolescents. As a result of its own efforts and these collaborations, the NIDDK is currently supporting a multi-faceted program of research at academic centers and small businesses to:

- Conduct clinical studies of portable artificial pancreas devices;
- Make stable, fast-acting formulations of insulin and another hormone important to managing blood glucose levels, glucagon;
- Improve glucose sensors' sensitivity and durability;
- Build and test devices that combine sensing and hormone delivery;
- Study physiological and behavioral factors to make artificial pancreas use easier; and
- Develop the next generation of glucose-sensitive technology.

Through recent initiatives, the NIDDK is also fostering research training of bioengineers and development of an interdisciplinary workforce to develop innovative technologies for diabetes treatment, including artificial pancreas systems. Notably, a significant portion of NIH-supported artificial pancreas research over the past 15 years has been made possible by funds from the *Special Statutory Funding Program for Type 1 Diabetes Research*.

JDRF supports its own program of research on the artificial pancreas, the Artificial Pancreas Project, which it launched in 2006. Over the years, the NIDDK has increased collaboration with JDRF and other

important funding entities, such as The Leona M. and Harry B. Helmsley Charitable Trust, to coordinate efforts so that there can be more efficient investment of resources to expedite advances in this field. For example, the NIDDK and JDRF are both funding sites in the Artificial Pancreas Consortium, a multi-site, international consortium of clinicians, engineers, and mathematicians who have tested early, hospital-based versions of an artificial pancreas and have started to test outpatient, wearable systems. Moreover, the NIDDK and JDRF have organized scientific panels of artificial pancreas investigators at the American Diabetes Association's annual Scientific Sessions, with the next one planned for June 2014.

The collaborative workshops organized by the NIDDK, the FDA, and JDRF, as well as the NIDDK and JDRF initiatives, have also inspired investment in artificial pancreas technologies by other, private foundations. For example, The Leona M. and Harry B. Helmsley Charitable Trust has recently launched initiatives on the artificial pancreas, such as the Trust's Automated Insulin Delivery Initiative. The Trust also funds the "bionic pancreas" project (as described later).

As a result of research investments and collaborative activities to promote artificial pancreas technologies, there has been rapid progress in the past few years toward achieving effective, wearable systems. For example, in just the last year:

- *"Low glucose suspend" devices:* The objective of these devices is to temporarily shut off insulin delivery when circulating glucose levels fall below a set threshold, to help prevent episodes of dangerously low blood glucose levels—an important aspect of artificial pancreas functionality. A recently published clinical study supported by industry (Medtronic) demonstrated that hypoglycemia events were less frequent, and events at night were less severe and shorter in duration, in patients using a glucose-sensor augmented low glucose suspend device at home. In September 2013, the FDA approved the Medtronic Minimed 530G, the device that was used in this trial, for use by people with diabetes 16 years of age and older. This is the first example of an artificial pancreas technology approved under the FDA guidance released in November 2012.
- *"Diabetes Assistant (DiAs)":* A number of investigators are developing and testing systems that close the loop between glucose sensing and insulin delivery using smartphone based technology, which would make the system practical for use outside of a hospital setting. A recently published study of one such system, the DiAs, which uses an Android-based smartphone, has demonstrated the feasibility of its use to control blood glucose levels in a hotel-based outpatient setting. This effort has been supported by the NIDDK and JDRF *(see also "Smartphone Technology Advances Progress Toward the Development of an Artificial Pancreas for People with Type 1 Diabetes" in this chapter).*
- *Bihormonal bionic pancreas:* To more fully recapitulate the hormonal controls of blood glucose levels lost in type 1 diabetes, some researchers are already working on systems that include both insulin, which lowers blood glucose levels, and glucagon, which raises them. Researchers working on a bihormonal bionic artificial pancreas based on an iPhone platform recently completed two outpatient studies in adults and children, with encouraging results. The "bionic pancreas" effort has received support from the NIDDK, JDRF, and The Leona M. and Harry B. Helmsley Charitable Trust, among others.

In concert with academia and industry, the NIDDK/NIH, the FDA, and JDRF have collectively catalyzed very intense and productive activity in the field of artificial pancreas research. This joint commitment by public and private institutions to an active role in the development of an artificial pancreas has fostered remarkable progress in recent years. Looking ahead, it is anticipated that these collaborative efforts will continue to lead to new successes in harnessing this new technology to improve the lives of people with diabetes.

# *Nobel Prize Honors Discoveries About the Transport System in Cells*

**Dr. James E. Rothman, 2013 Nobel Laureate.**
***Photo credit: Harold Shapiro, Yale University.***

One of the winners of the 2013 Nobel Prize in Physiology or Medicine is Dr. James E. Rothman, an NIDDK grantee. Currently a professor at Yale University, Dr. Rothman has received funding from several NIH Institutes, and much of the research that earned him the Nobel Prize was supported by a longstanding NIDDK grant that began in 1980. He has served on NIDDK's National Advisory Council.

He shares the Nobel Prize with two other scientists, Drs. Randy W. Schekman and Thomas C. Südhof, also both NIH grantees who have received funding from other Institutes.

Dr. Rothman was honored for his discovery of the machinery that regulates the traffic of small membrane-enclosed shuttles, called vesicles, which transport molecular cargo from one compartment within a cell to another, and between a cell and its environment. Exquisitely organized, this vesicle transport system underlies extraordinarily diverse biological processes critical for health, as vesicles carry hormones, signaling molecules for the nervous system, and other vital cargo. Defects in the process are associated with diabetes, neurologic diseases, and other adverse health conditions. Dr. Rothman's research is notable both for his landmark discoveries and for the pioneering experimental approach he took amidst an atmosphere of skepticism decades ago. His strategy was to break open cells and mix various cellular materials back together to try to reconstitute transport in a test tube; if that worked, he could then purify the necessary components of the transport machinery from the mixture to learn their identity. Many scientists at the time, however, believed that vesicles, outside the orderly confines of a cell, would not find the right target destination. But the approach worked, and Dr. Rothman and members of his laboratory went on to identify the machinery integral to this process, including a group of proteins they called SNAREs. Embedded in the membranes that surround vesicles and other cellular compartments, different SNAREs interact selectively so that vesicles dock at the correct destination. The SNAREs then promote fusion of the vesicle and target membranes, allowing release of the cargo. Since his groundbreaking findings years ago, Dr. Rothman's research has continued to yield new insights into this essential biological transport system.

The three scientists presented their Nobel Lectures in Stockholm on December 7, and received their awards on December 10, 2013.

# *NIDDK Scientist Recognized for Outstanding Contributions to Diabetes Research and Mentorship*

NIDDK Director Dr. Griffin P. Rodgers (left) and Dr. Peter H. Bennett (right) at Dr. Bennett's NIH Grand Rounds lecture in October 2013. ***Photo credit: Maria Maslennikov.***

Dr. Peter H. Bennett accepts the first Harold Hamm International Prize for Biomedical Research in Diabetes in October 2013. ***Photo courtesy of the Harold Hamm Diabetes Center.***

Scientist Emeritus and former Chief of the NIDDK intramural Phoenix Epidemiology and Clinical Research Branch (PECRB), Dr. Peter H. Bennett, received two prestigious awards in 2013 in recognition of his enormous impact on the field of diabetes research and his training and mentorship of diabetes investigators.

In recognition of his many accomplishments, on October 28, 2013, Dr. Bennett was the inaugural recipient of the $250,000 Harold Hamm International Prize for Biomedical Research in Diabetes. This prize recognizes innovation in the field of diabetes research with an emphasis on progress toward a cure. Awarded by the Harold Hamm Diabetes Center at the University of Oklahoma, the prize celebrates the scientific achievements of an outstanding researcher, team of researchers, or research institution selected by a rotating jury of national and international leaders in the diabetes community. Dr. Bennett also received the American Diabetes Association (ADA) 2013 Albert Renold Award at the ADA's 73rd Scientific Sessions in June 2013. The award is one of the ADA's highest scientific honors, given annually to an individual who has made a significant impact as a mentor of diabetes researchers and/or as a facilitator of a community of diabetes investigators. In addition to establishing a robust research program within the PECRB and providing training to hundreds of investigators worldwide, Dr. Bennett has directly mentored more than 50 scientists, many of whom now hold leadership positions in academic and federal institutions focused on diabetes and its complications.

Dr. Bennett's work on type 2 diabetes began in the 1960s, a time when little was known about the disease and nothing was known about its risk factors. Following his medical education at Victoria University of Manchester, United Kingdom, Dr. Bennett joined the NIDDK, which began conducting cooperative research on diabetes with the Gila River Indian Community in 1965, after scientists discovered the high prevalence of type 2 diabetes in this population. For over 30 years, glucose tolerance tests were given to almost every Pima Indian five years of age or older every two years. Results showed the Arizona Pima Indians had the highest prevalence of type 2 diabetes of any group in the world—including the genetically similar Mexican Pima Indians—leading Dr. Bennett to conclude that

environmental factors play a role in the prevalence of type 2 diabetes. As this multi-faceted study moved forward, he found that low physical activity and obesity were risk factors for the disease. He identified insulin resistance as another risk factor. Dr. Bennett's research led directly to new, evidence-based criteria for diagnosing type 2 diabetes and a high-risk prediabetic state, impaired glucose tolerance. All of these findings applied far beyond the Pima population, dramatically changing the diabetes landscape and setting the stage for clinical trials to prevent or delay type 2 diabetes in people at high risk, such as the landmark NIDDK-led Diabetes Prevention Program.

Through the long-running study in partnership with the Pima Indians, Dr. Bennett also found that children whose parents had diabetes were more likely to develop diabetes earlier in life and that breastfeeding prevented the early development of diabetes. Later, it emerged that diabetes during pregnancy conferred a greatly increased risk of early-onset diabetes to offspring—a finding that has been especially important to improving management of diabetes and its risk factors for mothers and their children, and which helped pave the way to ongoing studies of epigenetic factors during intrauterine development that predispose the offspring to obesity, type 2 diabetes, and other metabolic problems later in life.

Dr. Bennett's achievements in the field of diabetes research continue to be the foundation for the prevention, diagnosis, and treatment of type 2 diabetes and its complications. According to Dr. Clifton Bogardus, his long-time colleague and current Chief of the PECRB, "The contributions made by Dr. Bennett, in close collaboration with the Gila River Indian Community, to the understanding of the etiology and pathogenesis of type 2 diabetes have greatly influenced methods for the prevention and treatment of this disease worldwide and cannot be overstated. Equally important, he has trained and mentored countless numbers of scientists both within the NIDDK and elsewhere that will have a lasting legacy in the field of metabolism for decades. He was able to make these extraordinary achievements not just due to his great intellect and scientific acumen, but also due to his humility, collegiality, and cultural sensitivity that made it possible to work closely with the Pimas and collaborators around the world."

*This feature was adapted from an article by Mr. Eric Bock that originally appeared in the January 2014 edition of the* NIH Record.

# *NIDDK Director Testifies on Type 1 Diabetes Research*

On July 10, 2013, NIDDK Director Dr. Griffin P. Rodgers testified about progress in type 1 diabetes research before the Senate Special Committee on Aging, which is led by Chairman Bill Nelson (D-FL) and Ranking Member Susan Collins (R-ME). The hearing, entitled "Diabetes Research: Reducing the Burden of Diabetes at All Ages and Stages," was held in conjunction with the Children's Congress, an event sponsored every two years by JDRF (formerly the Juvenile Diabetes Research Foundation). In his testimony, Dr. Rodgers described research made possible by the *Special Statutory Funding Program for Type 1 Diabetes Research*, including progress from clinical trials testing approaches to delay or prevent type 1 diabetes, and progress toward the development of an artificial pancreas—a device to automate blood glucose sensing and insulin administration. The NIDDK administers the *Special Program* on behalf of the HHS Secretary.

Testifying with Dr. Rodgers were National Basketball Association star Ray Allen and his six-year-old son, Walker, who was diagnosed with type 1 diabetes at 17 months of age; Emmy Award-winning actress Jean Smart, who was diagnosed with the disease at age 13; JDRF President and CEO Jeffrey Brewer, also the father of a child with type 1 diabetes; and 14-year-old Quinn Ferguson, a JDRF Children's Congress delegate and participant in an NIDDK-supported clinical trial being conducted by Type 1 Diabetes TrialNet.

Shown at dais (left to right): Sen. Susan Collins (R-ME), Sen. Bill Nelson (D-FL), Sen. Elizabeth Warren (D-MA), Sen. Joe Donnelly (D-IN), and Sen. Jeanne Shaheen (D-NH). *Photo copyright: James T. Murray.*

Shown at table (left to right): Jean Smart, Walker Allen, Ray Allen, Dr. Griffin P. Rodgers, Jeffrey Brewer, and Quinn Ferguson. JDRF Children's Congress delegates sit in the foreground. *Photo copyright: Larry Lettera.*


NIDDK Director Dr. Griffin P. Rodgers. *Photo copyright: James T. Murray.*


Sen. Susan Collins and Sen. Bill Nelson. *Photo copyright: Geoff Hauschild.*


Sen. Joe Donnelly and Sen. Jeanne Shaheen. *Photo copyright: Geoff Hauschild.*

# STORY OF DISCOVERY

## *The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions And Complications Study: Thirty Years of Research That Has Improved the Lives of People with Type 1 Diabetes*

Diabetes slowly damages major organs in the body, such as the eyes, kidneys, and heart. Impressive research progress toward combating diabetes complications was achieved through a large clinical trial launched by the NIDDK in 1983. The Diabetes Control and Complications Trial (DCCT) was a multi-center clinical trial in 1,441 people ages 13 to 39 years with type 1 diabetes. It compared the effects of intensive versus conventional treatment of blood glucose levels on the development of microvascular complications (those affecting the small blood vessels in the eyes, kidneys, and nerves). Participants in the intensive treatment group kept their blood glucose levels and hemoglobin A1C (HbA1c) levels—which reflect average blood glucose levels over a two- to three-month period—as close to normal as safely possible through a regimen that included frequent monitoring of blood glucose and at least three insulin injections per day or use of an insulin pump. The study's conventional treatment, based on what was standard practice at the time the DCCT began, consisted of one or two insulin injections per day, with once-a-day urine or blood glucose testing.

The two treatment groups achieved markedly different average HbA1c levels over the course of the trial, and strikingly different rates of microvascular complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve damage, by 35 to 76 percent compared with what was then conventional treatment. It also demonstrated that HbA1c measurements could be used by health care providers and patients to monitor disease management by assessing blood glucose control and predicting risk of developing complications. The DCCT findings had a profound impact on clinical practice for the management of type 1 diabetes by leading to the development of clinical guidelines to recommend HbA1c targets for people with the disease; it also spurred the creation of the National Diabetes Education Program, co-led by the NIDDK and the Centers for Disease Control and Prevention (CDC), to disseminate the findings to patients and health care providers (*www.ndep.nih.gov*).

**Long-term Benefits of Intensive Blood Glucose Control**

Upon completion of the DCCT, participants who had received conventional treatment were taught the intensive treatment methods, and all were encouraged to use intensive treatment on their own, although the intervention itself stopped. Nearly all people who participated in the DCCT volunteered for the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study, which began in 1994. EDIC was established to determine the long-term outcomes of reducing exposure of the body's tissues and organs to high blood glucose levels.

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About five years after the transition to EDIC, blood glucose control (as measured by HbA1c levels) in the former intensive and conventional treatment groups converged to a similar level. This convergence occurred because of changes in glucose control in both groups. The level of blood glucose control in the participants from the former intensive treatment group was not quite as tight as it was during the DCCT, when they had the advantages of the clinical trial setting—although they were still able to achieve better glucose control on their own after the DCCT than they had before the trial. At the same time, those who were in the conventional treatment group during the DCCT began implementing a more intensive control regimen afterward, and thus improved their glucose control. With both groups now striving for intensive control on their own, the net result was that blood glucose control became nearly identical in the two groups during EDIC.

In 2002 and 2003, DCCT/EDIC investigators reported that, even though the two treatment groups had similar blood glucose control during EDIC, the former intensive treatment group had long-term health benefits from the finite period (averaging six and a half years) of intensive glucose control during DCCT: they continued to have reduced risk for microvascular complications seven to eight years after the end of DCCT compared to the former conventional treatment group. The phenomenon of long-lasting effects of a period of intensive or non-intensive glucose control has been termed "metabolic memory." More recent observations show that the differences in new cases of diabetic eye disease between participants who received the intensive treatment and those who received conventional treatment are beginning to narrow. Nonetheless, three decades after the start of DCCT, the two former treatment groups have substantially different rates of complications, suggesting that people with type 1 diabetes implement intensive glucose control as early in the course of the disease as possible.

An important unanswered research question after the DCCT ended was the effect of glucose control on cardiovascular disease (CVD), as CVD can take a long time to develop and the participants were too young to examine this complication during the DCCT. That question was answered in 2005—over 20 years from the start of the trial—when the DCCT/EDIC research group reported that intensive blood glucose control reduced the risk of nonfatal heart attack, stroke, or death due to CVD by 57 percent. These results showed for the first time that intensive control of blood glucose levels has long-term beneficial effects on CVD risk in people with type 1 diabetes. These findings are particularly significant because people with type 1 diabetes face a 10-fold increased risk of CVD death compared to the general age-matched population.[1,2]

Insights continue to emerge regarding the long-term benefits of early and intensive blood glucose control. In 2009, DCCT/EDIC researchers found that, after 30 years of diabetes, DCCT participants in the former intensive treatment group had about half the rate of eye damage compared to those in the former conventional treatment group (21 percent versus 50 percent). They also had lower rates of kidney damage (9 percent versus 25 percent) and cardiovascular events (9 percent versus 14 percent) compared to those in the former conventional treatment group. These findings suggest that with early intensive therapy to control blood glucose levels, the outlook for people with type 1 diabetes is better than ever.

More good news was reported in 2011 related to the long-term risk of developing kidney disease. During the DCCT, the participants were too young for researchers to examine the effect of glucose control on actual kidney disease, which (like CVD) can take a long time to develop. The researchers did find that at the end of DCCT, intensive therapy reduced a condition associated

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with kidney damage, called albuminuria. However, following the participants for longer timeframes in EDIC allowed the researchers to examine the development of kidney disease. In 2011, after an average 22-year follow up, DCCT/EDIC demonstrated that controlling blood glucose early in the course of disease not only continued to reduce albuminuria, but also decreased participants' long-term risk of developing kidney disease by 50 percent. This important finding showed that controlling blood glucose early in the course of type 1 diabetes yields huge dividends, preserving kidney function for decades.

In 2013, the DCCT/EDIC researchers and patient volunteers celebrated a remarkable 30 years of participation in research since the launch of the DCCT in 1983. To date, 95 percent of living DCCT patient volunteers continue to participate in EDIC. This unwavering dedication to research has transformed how type 1 diabetes is treated: when people with the disease visit their doctors today, the advice that they receive stems directly from DCCT/EDIC research findings—a testament to the impact that DCCT/EDIC research has had on a public health level.

**Research To Combat Hypoglycemia and To Help People Achieve Recommended Levels of Blood Glucose Control**

Even though the results of DCCT/EDIC show that intensive glucose control is beneficial for long-term prevention of complications, type 1 diabetes is a burdensome disease to manage. It requires patients (or parents of young children) to check their blood glucose levels with finger sticks, monitor food intake and physical activity levels, and administer insulin. In addition, a severe limitation to the practice of intensive therapy is the potential for acute episodes of hypoglycemia, or low blood glucose. The immediate effects of hypoglycemia can be severe, including changes in cardiovascular and central nervous system function, cognitive impairment, increased risk for unintentional injury, coma, and death. Therefore, the DCCT/EDIC findings underscore the importance of research to develop new tools to help patients achieve recommended levels of glucose control with less risk of hypoglycemia.

NIDDK-supported researchers have already been successful in contributing to the development of U.S. Food and Drug Administration (FDA)-approved continuous glucose monitoring technology, which may enable better glucose control by providing patients with real-time measurements of glucose levels every few minutes and sounding alarms when glucose levels are too high or too low. The NIDDK also supports research to develop artificial pancreas technology, which would integrate continuous glucose monitoring with automated insulin delivery based on the glucose data, representing an important current opportunity to help people with diabetes implement intensive blood glucose control. Other research is pursuing strategies to develop approaches to replace or regenerate the body's insulin-producing beta cells, which are lost in type 1 diabetes, as a potential cure for the disease. Through these multi-faceted approaches, the NIDDK remains committed to helping people with type 1 diabetes safely achieve good blood glucose control with less burden, to realize the full benefits of the DCCT/EDIC findings.

**Benefits for Type 1 Diabetes and Beyond**

Findings from the DCCT/EDIC have transformed the management of type 1 diabetes, but have also benefitted people with type 2 diabetes. For example, the results of DCCT/EDIC stimulated the conduct of trials assessing the role of blood glucose control in type 2 diabetes. These trials have informed clinical guidelines developed by the American Diabetes Association and other groups, which now include HbA1c targets for most people with diabetes.

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However, lack of standardization of HbA1c tests made it difficult to utilize these targets in medical practice. In other words, there were many different types of HbA1c tests being used that gave varied results, so results were not comparable from one laboratory to another. To address this gap, the NIDDK and the CDC launched the National Glycohemoglobin Standardization Program in 1996 to improve the standardization and reliability in measures of HbA1c. The standardization effort has been a great success: variability of HbA1c test results has steadily reduced, and the availability of a standardized testing method has allowed international experts to recommend expanding the use of HbA1c beyond monitoring of blood glucose control during treatment to use it as a more convenient test to diagnose type 2 diabetes. Thus, standardization of the HbA1c test has not only benefited management of type 1 and type 2 diabetes by enabling health care providers and patients to accurately and meaningfully assess blood glucose control and risk for complications, but has expanded the utility of the HbA1c test to be used for diagnosis of type 2 diabetes.

In addition, the DCCT established the value of HbA1c as an outcome measure for clinical trials in both type 1 and type 2 diabetes. This has dramatically shortened the cost and duration of trials for new therapies because improvements in HbA1c levels are detected long before changes in complications become apparent. The use of HbA1c as an outcome measure was the basis for FDA approval of approximately 10 new classes of drugs for type 2 diabetes, as well as for improved forms of insulin. These are just a few examples of the far-reaching benefits that have stemmed from DCCT/EDIC research.

**A Long-term Investment in Research Improves the Lives of People with Type 1 Diabetes**

The DCCT/EDIC demonstrates how a long-term investment in research has had a profound impact on the health of people with type 1 diabetes. Thirty years after the beginning of the DCCT, researchers are still demonstrating significant findings that continue to improve the care of people with type 1 diabetes and also have implications for people with type 2 diabetes. Because the cohort of DCCT patients was too young for examination of cardiovascular complications and kidney disease when the study began, the long-term follow up was necessary to assess the effect of intensive glucose control on these devastating and life-threatening diabetic complications. The research shows that the full benefits of treatment may not be seen for decades, especially for complications of diabetes, which can progress slowly but have devastating consequences. It has only been through 30 years of steadfast dedication of the DCCT/EDIC research group and patient volunteers that these benefits continue to emerge. They are a key reason why people with type 1 diabetes are living longer, healthier lives than ever before.


[1] *Krolewski AS, Kosinski EJ, Warram JH, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 59: 750-755, 1987.*

[2] *Dorman JS, Laporte RE, Kuller LH, et al. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: mortality results. Diabetes 33: 271-276, 1984.*

# SCIENTIFIC PRESENTATION

## Genomics of Type 2 Diabetes and Metabolic Syndrome: Lessons from a Founder Population

*Dr. Alan R. Shuldiner*

*Dr. Alan R. Shuldiner is the John L. Whitehurst Professor, Associate Dean for Personalized Medicine, and Director of the interdepartmental Program for Personalized and Genomic Medicine at the University of Maryland School of Medicine, as well as co-Director of the University of Maryland Clinical and Translational Research Institute. He received his M.D. from Harvard Medical School, and completed his residency in internal medicine at Columbia-Presbyterian Hospital in New York, later becoming a Medical and Senior Staff Fellow in Endocrinology and Metabolism in the NIDDK's Intramural Research Program. Through projects in many areas, and in particular through genomic research with the Old Order Amish of Pennsylvania, Dr. Shuldiner has made important contributions to understanding the molecular causes of type 2 diabetes and cardiovascular disease. In his presentation, he described some of the discoveries that have stemmed from his work with the Amish.*

**Studying Chronic Disease in the Old Order Amish**

Dr. Shuldiner began by recognizing the multidisciplinary team of scientists with whom he works. Describing his research focus, he introduced the interaction among genes and the environment in the development of type 2 diabetes; cardiovascular disease (heart disease and stroke); and the metabolic syndrome, a constellation of cardiovascular risk factors, which includes insulin resistance and diabetes. He then turned to his studies of the genetics of these complex diseases, highlighting his longstanding partnership with the Old Order Amish community, whose participation has made this research possible.

Explaining that the Amish are an excellent population for studying complex genetic metabolic diseases, he described attributes of their lifestyle and genetics that have facilitated this research. They have a traditional lifestyle that has changed little since the 18th century, with low use of medications, no cars, television, telephones, or even electricity; and they rely on manual labor and a diet composed largely, though not exclusively, of foods grown and prepared within the community. This relatively homogeneous lifestyle helps to minimize some problems common to other large genomic studies: the potential that any particular gene variant might have variable effects among people with widely differing exposure to environmental factors that contribute to or protect from chronic disease.

Moreover, the Amish represent a "closed founder community," which is to say they began as a relatively small population who immigrated to this country and, as their population has grown, they have remained cohesive, with little or no intermarriage with outside groups. Thus, while there is genetic variation among the Amish, they have less overall genetic complexity than larger groups. Among people in a more heterogeneous population (all Americans of European descent, for example), there may be many variations in a particular, important gene: some conferring disease risk, some conferring disease protection, and some that have no effect. Thus, the genetic homogeneity of the Amish simplifies the process of identifying disease-affecting genetic differences among them in two ways. First, high disease risk variants that are very rare in the general population may have increased in

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frequency in the Amish, making them easier to identify and study. Second, most of the common variants that have a smaller effect on disease risk that are present in the general population also exist in the Amish. These risk alleles may have more consistent effects in populations that are more homogeneous with respect to genetics and lifestyle, such as the Amish.

Because Amish families typically have many children, researchers can more easily detect inheritance patterns of genetic traits. Family members also tend to live close to each other, and this proximity has enabled Dr. Shuldiner's team to recruit several thousand Amish individuals as participants in the research. Another characteristic of the Amish—that they have maintained extensive genealogical records dating to the 18th century—has been of great value to genetic research by describing how community members are related to one another, and helping to determine the lifetime impact of specific traits.

Dr. Shuldiner noted that his work has also benefitted from the University of Maryland Amish Research Clinic, a state-of-the-art facility that he helped establish in the heart of Amish Country in Pennsylvania, which has greatly enhanced collaboration between researchers and the Amish people, and has been instrumental for making the discoveries outlined below.

**A Gene with a Profound Effect on a Key Class of Fats in the Blood**

Thanks to the first line of research Dr. Shuldiner described, we now know it may one day be possible to treat or stave off coronary artery disease by inhibiting the action of a factor in blood involved in transport of certain fats in the body. The body stores most fat in chemical compounds called triglycerides. Both high fasting levels of triglycerides and poor clearance of triglycerides after a high-fat meal are known to be risk factors for heart attacks and stroke; and these fasting and post-meal triglyceride levels vary considerably among different people, an observation long thought to be at least partially explained by genetic variation. Dr. Shuldiner described how studying the Amish bolstered this hypothesis through the discovery of a mutation in one of the triglyceride carrier proteins.

After giving a set amount of a milkshake-like high-fat drink to more than 800 Amish men and women, Dr. Shuldiner and colleagues measured the beverage's effect on blood triglyceride levels over the next few hours. The researchers found considerable variation in the resulting triglyceride load in blood samples from different participants—just as would have been expected in a less homogeneous population—suggesting that some individuals in the Amish population may harbor genes that promote rapid clearance of dietary fat, while the genes of other Amish people may lead to average or slower triglyceride clearance.

The researchers then used a powerful genetic and computational method—a genome-wide association study—to probe the participants' genomes for gene variants that correlated with very good or very poor triglyceride clearance. In this way, they discovered that a genetic variation (mutation) that inactivates the gene *APOC3* was strongly associated with low triglyceride levels. Most Amish people—and most everyone else—have two working copies of *APOC3*. Close examination, however, revealed that about five percent of the Amish have the triglyceride-lowering mutation identified through this study in one of their *APOC3* gene copies. (The mutation is much rarer among the non-Amish.) Because triglycerides, like other fats, are not soluble in water, the body utilizes special carriers called lipoproteins for moving triglycerides in the bloodstream. One of the triglyceride-carrier molecules, Apo C-III, is

the product of the *APOC3* gene. As might be expected, having one normal and one mutant *APOC3* effectively cuts in half the amount of Apo C-III and triglycerides in the blood stream.

Rather than conferring an illness, as many mutations in other genes do, this *APOC3* mutation seems to help those who have it maintain healthier serum triglyceride levels. In fact, the mutation also seems to inhibit development of another marker of heart disease risk, calcification of the coronary arteries. However, despite these apparent benefits, it remained unclear whether the mutation helps those who have it live longer. To get a better handle on the mutation's overall effect on health, the researchers turned to the extensive birth and death records maintained by the Amish. They found that the mutation actually seems to help extend life: almost 1 in 4 Amish people inferred to have had a copy of the *APOC3* mutation lived to be at least 90, compared to less than 1 in 10 of those who lacked it.

The fact that these observations—that having low Apo C-III levels reduces heart disease risk factors and that it seems to lengthen life—were made in a human population suggests that a pharmaceutical approach to inhibit Apo C-III action or to lower the protein's levels may be safe and effective for treating or preventing heart disease. Indeed, Dr. Shuldiner noted that another team of researchers, at a pharmaceutical company, recently published the results of a preliminary, short-term test of one method for lowering Apo C-III, in which they showed significant reduction of the participants' triglyceride levels. Further research will be needed to determine whether the approach is safe and effective for prevention or treatment of cardiovascular disease in long-term use, and whether different diets may be healthy for different people, depending on their genetics—an important example of the emerging field of "nutrigenomics."

**A Mutation That Renders an Otherwise Valuable Medicine Ineffective for Some People**

Dr. Shuldiner next described research that led to the discovery of a mutation that keeps many people from benefiting from clopidogrel (brand name Plavix™), a drug prescribed to help prevent recurrence of heart attacks (myocardial infarctions) and strokes in people who have experienced such an event. Heart attacks and strokes often result from clots that form inside blood vessels, limiting blood flow to the heart or the brain, respectively. Clots are formed by blood cells called platelets, and are critical for staunching blood flow from cuts and scrapes. Clopidogrel binds to a specific protein on the surface of platelets, preventing them from aggregating to form a clot and thus reducing the occurrence of undesirable clotting within the blood stream that can lead to a heart attack or stroke. In most people, clopidogrel does this quite effectively. But there is considerable variation in the capacity of the drug to inhibit platelet aggregation in different individuals, so that some people seem not to benefit from the medication.

Dr. Shuldiner and his colleagues measured platelet aggregation in more than 650 Amish volunteers before and after one week of clopidogrel therapy, and found that the variable nature of the clopidogrel response is also seen among the Amish: some had a strong response to clopidogrel, while in others the medicine had almost no impact on clotting. Through a statistical approach that again allowed them to utilize information from the Amish genealogical records to determine how the participants were related to one another, the researchers were able to determine that about 70 percent of the variation in clopidogrel response was the result of genetic factors. This observation suggests that if the genes affecting the clopidogrel response can be identified, it might be beneficial to employ a "pharmacogenomic" treatment

strategy—using genetic tests to determine whether clopidogrel or newer, more costly anti-platelet drugs will be best for a particular patient.

By utilizing another genome-wide association approach, Dr. Shuldiner and his fellow researchers were able to identify one such gene, *CYP2C19*, and a mutation in the gene that makes clopidogrel dramatically less effective. In the absence of clopidogrel, they found that platelet function is normal whether or not someone has the mutation. But people with one normal and one mutant *CYP2C19* gene responded significantly less strongly to the medicine than those with two normal copies; and in people with two mutant copies of the gene, clopidogrel had almost no effect. Based on pharmacological studies of others, it was discovered that the normal product of the *CYP2C19* gene is a protein that converts clopidogrel from a biologically inactive compound into its effective form. Thus, in people lacking the protein, clopidogrel remains effectively inert, and in people with half as much of the protein as others, an intermediate amount of the medicine is converted into its active, platelet-inhibiting form.

Unlike the *APOC3* mutation, which is extremely rare among the non-Amish, the *CYP2C19* mutation is fairly common: about one-third to one-half of non-Amish individuals have at least one copy, and have about a 2.4-fold higher risk of heart attack or stroke than a person with no *CYP2C19* mutation taking clopidogrel.

The U.S. Food and Drug Administration responded to these findings and similar findings by other researchers by requiring clopidogrel manufacturers to change the labeling on the medication's packaging to note this effect, as well as the fact that tests for the presence of the *CYP2C19* mutation are available, and that other drugs may be more effective for people who have it.

Dr. Shuldiner noted that as significant an effect as the mutation has, however, it accounts for just 12 percent of the overall variation in clopidogrel-induced changes in blood clotting, so more work is needed to identify other mediators of patient response to the medicine. Because the drug is highly effective for preventing heart attack and stroke in most people at high risk for such events, and is also safe and inexpensive relative to alternatives, clopidogrel—along with low-dose aspirin—remains a widespread and highly beneficial anti-platelet therapy for most people at high risk of heart attack or stroke.

**Conclusion: Type 2 Diabetes and the Old Order Amish**

In ongoing research, Dr. Shuldiner and colleagues are shedding new light on the genetic underpinnings of type 2 diabetes. Through their Amish Family Diabetes Study and other epidemiological research, they found that Amish children tend to be leaner and more physically active than other American children, but that Amish adults are about as likely as other Americans to be obese. Furthermore, while the Amish are actually more likely than other groups to have prediabetes, they are less likely to develop type 2 diabetes. A reasonable hypothesis to explain these findings is that the Amish population harbors significant genetic risk for type 2 diabetes, but that their physically active lifestyle offers them some protection from the disease.

Indeed, genome-wide analysis revealed evidence that genetic variation among the Amish does markedly affect the probability of developing type 2 diabetes, and it is enticing to speculate that one or more genetic variants found to be associated with type 2 diabetes among the Amish might have particularly potent effects, since they would be capable of overcoming the protective qualities of the active Amish lifestyle.

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Going forward, the team of scientists aims to elucidate the physiological basis for these variations in risk.

Dr. Shuldiner concluded by discussing how the analysis of such genetic variants in the Amish can often shed light on the molecular mechanisms of metabolic regulation in all people, help optimize treatment approaches for type 2 diabetes and cardiovascular disease in individual patients, and suggest potential new targets for therapeutic intervention.

# PATIENT PROFILE

## Wesley Wilson

*A Lifetime of Type 1 Diabetes May Hold a Key to the Future*

**Wesley Wilson and his family. Left to right: Kate, Patrick, Justin, Luella, Wesley, Beth, Roger, and Kathleen.**

Wesley Wilson has a lot to celebrate these days. He and his wife recently celebrated their 80th birthdays with their family, friends, and Wesley's doctors. Although he jokingly admits to wearing out some of the doctors he's seen since moving to Montana in 1963, Wesley's doctors are welcome fixtures at his parties, especially at the one celebrating his receipt of the Joslin 50-Year Medal, an award for living with type 1 diabetes for 50 years. "When I got my 50-Year Medal, we had a big party. It was nice to have something to celebrate in regards to diabetes," says Wesley.

Type 1 diabetes is an autoimmune disease in which the immune system destroys the cells in the pancreas that make insulin. People with the disease must carefully monitor blood sugar levels and administer insulin, either through injections or an insulin pump. Despite vigilance in management of their diabetes, it is difficult for people to achieve near normal blood sugar levels and to prevent the complications of the disease.

The Joslin Medalist Program at the Joslin Diabetes Center in Boston, Massachusetts, began awarding medals to people with type 1 diabetes in 1948, with the hope that they would serve as incentive to those committed to good, albeit challenging, diabetes care. At first, the Program awarded 25-Year Medals but, with improvements in care and treatment, Joslin was able to begin awarding the 50-Year Medal in 1970, the 75-Year Medal in 1996, and the 80-Year Medal in 2013. To date, Joslin has presented over 4,000 50-Year Medals, 68 75-Year Medals, and 4 80-Year Medals. Given the challenges that living with type 1 diabetes provides and the devastating complications that it can cause, these medalists are a special group to be celebrated.

*"It was nice to have something to celebrate in regards to diabetes," says Wesley, of his Joslin 50-Year Medal.*

**The Doctor Becomes a Patient**

Wesley was diagnosed with type 1 diabetes during his second year of medical school in 1956 and had been married just a few months earlier. "We got married in July and in the fall, my wife said you've been drinking a lot of water and urinating an awful lot." As a young medical student, Wesley hadn't had clinical experience, but his wife, who was a nurse at the time, encouraged him to go to a doctor. His blood sugar was high, and he was

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diagnosed with type 1 diabetes. Wesley recalls, "I was so involved with med school that, when I think back on it, it didn't seem to make a great impression on me. I mean I did realize that I had to change my lifestyle and take insulin, but I was just kind of going to sail along."

Then, in December, his class began to study pathology, and the lectures focused on diabetes and its complications. To this day he remembers those lectures very well. "They [the lectures] are imprinted indelibly in my head. At that time it was taught that folks with diabetes had a life expectancy about a third as long as the usual population and then, of course, it was always marked by complications." Wesley remembers being taught that, "there was nothing you could do to prevent eye, kidney, and heart disease. So the lecture had more of an impact on me than just the initial diagnosis, including that whatever you did didn't make much difference."

But it wasn't long before Wesley was introduced to the idea that what he did could make a difference. He began his residency at the University of Oregon and, once again, credits his wife because she was working at a hospital linked to the Portland Diabetes Center. A doctor there had trained at the Joslin Diabetes Center and was a believer in tight sugar control even before blood sugar testing technology became available. "We had classes on carbohydrates and how to adjust the insulin to try to match the carbohydrate content in the meal. I think that was the first effort to try and achieve some degree of control," remembers Wesley.

Subsequent research has shown that Wesley's doctor was correct about the importance of tight sugar control—the NIDDK's Diabetes Control and Complications Trial (DCCT) demonstrated in 1993 that achieving blood sugar control as close to normal as safely possible reduced the risk of eye, kidney, and nerve complications associated with type 1 diabetes. In 2005, the DCCT's follow-on study, the Epidemiology of Diabetes Interventions and Complications, demonstrated that intensive blood sugar control could also reduce the risk of cardiovascular disease-related complications. These results revolutionized treatment of type 1 diabetes and greatly improved the prognosis of people with the disease.

**The Joslin 50-Year Medalist Study**

Wesley has seen the complications of diabetes; after training in hematology—the study of blood—and oncology, he switched his specialty to diabetes, after the DCCT showed tight sugar control could reduce the risk of complications, providing care to people with type 1 or type 2 diabetes. Fortunately, Wesley has not had to deal with these complications as a result of his own type 1 diabetes, something that amazes him to this day. "To be able to go 50 years without really any significant complications is a little bit hard for me to believe. It's worth the celebration just for that reason." In fact, there are a number of medalists who have avoided the complications that usually accompany the disease. As Wesley notes, "I was at the medalist reunion and, while there are clearly people there who have complications, these people looked like any other bunch of old folks. So there's something that sets that group apart, and I think that's the real question. There must be something detectable or measurable that would explain the avoidance of complications in some people while other people have so many of them. We need to find out what it is."

The 50-year medalists represent a unique collection of individuals with long-standing type 1 diabetes who have mostly avoided the complications of the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), and heart that can accompany the disease. Individuals in this group may have certain

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factors—genetic, environmental, psychological, and physiological—that have contributed to their survival with long-term diabetes and protected them from the disease's complications. A group of investigators at Joslin agree that the medalists may hold keys to preventing the complications of diabetes. They invited the Joslin's 50-year medalists to participate in a clinical research study, the 50-Year Medalist Study, examining the outcomes of long-term type 1 diabetes and aiming to identify factor(s) that contribute to the longevity of this unique group and lead to resistance to complications.

*Of his participation in the Joslin 50-Year Medalist Study, which seeks to identify factors that contribute to longevity and resistance to diabetes complications, Wesley says "I think that's the key to get the information about what to do [to combat type 1 diabetes]. It's the future."*

Wesley didn't hesitate to participate in the study and feels that participation hasn't been too taxing. "It's not complicated," he responds when asked about his role in the study, "[I need to] be available to come back and get checked out occasionally." But, Wesley's participation goes well beyond that. He will make a special contribution to this research study some day in the future by donating some of his tissues post-mortem for analysis. Wesley feels that this contribution is critical: "I think that's the key to get the information about what to do [to combat type 1 diabetes]. It's the future," he explains, noting that type 1 diabetes is increasing in its frequency. By studying tissues like Wesley's, scientists hope to uncover new ways to prevent, reverse, and treat type 1 diabetes and its complications. "It's one thing I can do," shares Wesley, "If any part of my body would help understand that or identify [a factor/factors], I think that would be a great thing to have."

**A Lifetime of Improvements in Diabetes Care**

In his over 50 years with type 1 diabetes, Wesley has seen significant change in treatment and care of the disease. At the time he was diagnosed, people could only check sugar levels with urine tests, which recognized high but not dangerously low sugar levels and reflected past, not current, sugar levels; more reliable methods for testing sugar levels in the blood had not yet been developed. As Wesley explains, at that time, "you just tried to avoid the extremes, which in a way made sense because we had no way of checking blood sugars. I think everyone I knew who resorted to doing urine tests realized it was of no benefit to tell you what your blood sugar was at the time. You tended not to pay any attention to the urine test."

For Wesley the big step was when blood sugar testing arrived: "That is the big development as far as I'm concerned," he says, "because it allows control. I tell people that's the greatest gift that we've had." Today people with type 1 diabetes can wear continuous glucose monitors that provide real time information about a person's blood sugar levels and insulin pumps that can provide doses of insulin without injections. Artificial pancreas technologies that link these monitors and pumps and allow automatic release of insulin in response to high blood sugar readings are in clinical tests, and a device that suspends delivery of insulin when blood sugar levels drop dangerously low has already been approved by the U.S. Food and Drug Administration. In addition, certified diabetes educators have come on the scene to help with giving advice on the day-to-day management of diabetes.

Wesley has also loved physical activity and the outdoors, especially the mountains of Montana, and feels that exercise is vital to his health and managing his diabetes. "Daily exercise can be worked into any schedule," he shares, "everyone, especially those

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with diabetes, can find something they enjoy and can do almost every day." Wesley has found enjoyment in simple activities, like walking the family dog and gardening, and in more challenging ones, like scaling the highest peaks in Montana and Idaho. He and his wife also love to run and have participated in everything from local fun runs to marathons. Wesley even ran while he was practicing medicine, slipping it into his busy schedule—"It allowed me to burn up a lot of energy in a short time," he explains. Even still, Wesley is also quick to credit his good health to luck and his strong partner in the journey, his wife.

So, has diabetes slowed Wesley down at all? "I think it has taken the edge off things," he shares, "but if you are determined you can do things anyways. I think the main trouble is that you never can really forget about it. You can't just say I'm not going to take my insulin for a few days. Unfortunately, it's always there." But Wesley sees a lot of hope for people diagnosed with type 1 diabetes today in all the improvements in technology, changes in practice resulting from research results, and people available to help. The outlook is encouraging, especially with the promise the Joslin 50-Year Medalist Study holds to uncover protective factors for type 1 diabetes and its complications. He muses, "These days there are going to be far too many applicants for the 50-year award medals than Joslin is going to be able to give out because of the fact that people can now control their diabetes." That is cause for celebration.

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## Paul and Tim Daly

*Looking Out for One Another and Taking on Type 2 Diabetes*

Paul Daly (left) and Tim Daly (right). ***Photo by Roberta Daly.***

Paul and Tim Daly have always been close. Identical twins from a close-knit family, they served in the Army together, attended the same technology school post-enlistment, and worked together, later, at Tim's video store in Framingham, Massachusetts. As they tell it, having a twin brother was "like being born with a best friend," and looking after one another was a lesson they learned early. "One of our uncles said 'look, you always back up your brother,'" Paul explains. "And that stayed with me. Whether you're with friends or wherever, you always back each other up. It's like the Golden Rule."

Decades later, it's a rule they still follow. Of course, while the rule may once have meant uniting to confront a schoolyard bully, today it more often means confronting diabetes.

In the mid-1990s, Paul's doctor told him he had elevated blood glucose that put him at risk for the disease. "The mistake I made was ignore them, 'cause I felt good," Paul says ruefully. He thought at the time that "risk for diabetes" meant "I wasn't sick, so I didn't need to worry about it." But about 6 months later, he found he was thirsty all the time. He learned from his doctor he had gone on to develop type 2 diabetes, and he knew he had to tell Tim as soon as possible, to make sure Tim knew "risk for diabetes" was something he *did* have to worry about.

*When his doctor told him he was at risk for type 2 diabetes, "the mistake I made was ignore them, 'cause I felt good," Paul says ruefully. When he later developed the disease, he told his twin brother, Tim, as soon as possible, to make sure Tim knew "risk for diabetes" was something he* did *have to worry about.*

After Paul relayed the news of his diagnosis, a family friend told Tim about a brochure she'd seen for a new study that was recruiting participants to see if type 2 diabetes could be prevented or delayed. Tim was struck by the timing, hearing about the study so soon after finding out about Paul's diabetes. "If this isn't a message from God…" he recalls thinking. He wasted no time before calling to set up an appointment with the staff of the just begun Diabetes Prevention Program (DPP). Through blood tests provided by the study, he found out he was in much the same place Paul had been 6 months before: he did not yet have diabetes, but he was dangerously close. The lesson of Paul's experience was not lost

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on Tim, who readily agreed to enroll, thus becoming one of the DPP's earliest participants.

**The Diabetes Prevention Program**

The DPP, led by NIDDK with additional support from other NIH Institutes and Centers, the Centers for Disease Control and Prevention, the Indian Health Service, and non-governmental organizations, recruited adult volunteers at 27 clinical centers around the United States. Participants were randomly divided into different treatment groups. The first group, called the lifestyle intervention group, received intensive training in diet, physical activity, and behavior modification. By eating less fat and fewer calories and doing moderate exercise, such as brisk walking, for a total of 150 minutes a week, they aimed to lose 7 percent of their body weight and maintain that loss. This intervention was based on extensive behavioral research that suggested it would be a sustainable approach to modest weight loss for a high proportion of participants. The second group took the generic diabetes drug metformin twice a day. The third, a control group, received placebo pills instead of metformin. The metformin and placebo groups also received information about diet and exercise, but no intensive behavior change counseling. All 3,234 study participants were overweight or obese; and, although they did not have diabetes by the criteria used at the time, their fasting glucose levels were elevated, and they had impaired glucose tolerance (meaning their blood sugar remained elevated longer than normal after drinking water that contained a set quantity of glucose.) Forty-five percent of the participants belonged to racial and ethnic groups at increased risk for developing diabetes.

The study was a tremendous success. In fact, researchers announced the initial findings of the DPP in 2001, a year earlier than scheduled, because the results were so striking. The lifestyle intervention reduced participants' risk of developing diabetes by 58 percent, and was effective for both men and women, for all race/ethnic groups in the study, and for participants of different ages. Participants taking metformin lowered their risk of developing diabetes by 31 percent.

*"I started logging in everything I was eating, the exercise that I was doing," Tim says, and he added more exercise to his week and modified his diet. The attention to detail paid off.*

**Tim Daly's DPP Experience**

Tim was randomly assigned to the DPP lifestyle arm. "I started logging in everything I was eating, the exercise that I was doing," Tim says. "I weighed 200 lbs, so my goal weight was 186." He already exercised about 2 hours per week, playing basketball with friends—exercise Paul had not been getting, which may have contributed to the earlier onset of his diabetes. So Tim only had to add 30 minutes of brisk walking to get to the goal of 150 minutes. The diet portion was a bit more of an adaptation, but "my goal was 42 grams of fat/day. So I was focused on that—not the carbohydrates, just the fat. We'd go in restaurants and I had certain meals I'd picked out—that's what I'm going to have when I go to that restaurant." The attention to detail paid off: within 6 months, he'd reached his goal weight—and he continued to be diabetes-free.

Was it tough? "I didn't feel it was that difficult," Tim recalls. But sometimes his weight began to drift back up, and when that happened, a study coordinator found a powerful way to motivate him. "She said, 'Tim—do you realize I have people in the study and they'll go, "Oh, what's the point? My family has diabetes, I have family history—I'm going to get it. What's the point?"' and she'll go, 'Time out. I have a guy in the study whose twin brother has been

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diagnosed with diabetes. And so he's been in the study since 1996, and he's not diagnosed as diabetic.'" Tim certainly got the message: "Oh, God," he thought, "I've got to do my best!"

**The Diabetes Prevention Program Outcomes Study**

At the completion of the DPP, no one knew how long the interventions' benefits would endure, since the results were based on just 3 years of data. Therefore, after a "bridge" period from January to July 2002, when all participants learned the results and were offered a multi-session program explaining how to make the lifestyle changes, the Diabetes Prevention Program Outcomes Study (DPPOS) began, with most of the DPP volunteers taking part. DPPOS participants who received metformin during the DPP continue to receive metformin. The lifestyle intervention has also continued, albeit somewhat less intensively, for participants from the lifestyle arm who agreed to stay in for the DPPOS. In addition, classes encouraging adoption of the lifestyle changes were also made available to DPPOS participants from the metformin and placebo arms, but attendance was optional.

*"When my weight goes up, all the numbers go up… all the stuff you want to keep down."*

Through analysis of data collected from participants over an average of 10 years after their initial enrollment in the DPP, researchers were able to conclude in 2010 that the lifestyle intervention reduced the rate of developing type 2 diabetes by 34 percent during this time, compared with placebo. Importantly, study participants who received the lifestyle interventions in the DPP and DPPOS also had fewer cardiovascular risk factors, including lower blood pressure and triglyceride levels, despite needing fewer drugs to control their heart disease risk. Over the same 10 years, treatment with metformin reduced the rate of developing diabetes by 18 percent compared with placebo. Through DPPOS research we also now know that the lifestyle and metformin interventions were highly cost-effective: by helping keep the participants healthier than they would have been otherwise, the interventions reduced the participants' other (non-study associated) health care costs.

*Of exercise, Paul says, "Afterwards, always you have more energy; you just feel better mentally because you worked a little bit toward a goal." And like Tim, Paul has changed his diet for the better.*

So thanks to Tim and the many other former DPP participants who agreed to continue participating in research through the DPPOS, study scientists have learned a great deal about the long-term outcomes of the DPP interventions. And sticking with the program has also had tremendous benefits for Tim personally. "I go in twice a year now, and… historically… they have all the numbers. It's incredible. When my weight goes up, all the numbers go up: blood sugar, cholesterol—all the stuff you want to keep down. It was definitely related to my weight." Confronting those numbers helped Tim stay on-task, and keep taking good care of himself.

Tim's healthful lifestyle greatly slowed the gradual rise in blood glucose levels most people experience as they age, but did not arrest that rise completely. Thus, as judged by one test, Tim's blood glucose control has recently reached the range considered indicative of diabetes, and by DPPOS protocols, Tim

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is considered to have developed type 2 diabetes. From Tim's perspective, even though the DPP lifestyle intervention did not permanently prevent diabetes, it did help him remain free of this disease—and free of the challenges of managing it and related health complications—for 17 years after Paul's diagnosis. "With Tim jumping on it as soon as he found out—that made the difference," says Paul. Tim agrees: "It did!"

Further, the study—and the journey that began with Paul's diagnosis—imbued both men with the determination to remain as healthy and active as possible. Tim still exercises avidly. He plays golf with his buddies, and he doesn't use a cart. He and his wife also stay fit and active though a shared love of country line dancing. In addition, he recently started a new fitness program with his wife and one of his daughters, and reached his lowest weight in decades.

Paul, too, recognized the importance of adopting a healthier lifestyle. For fitness, he enjoys bicycling and walking on the beach. Both brothers have become great proponents of exercise. As Paul puts it, "Afterwards, always you have more energy; you just feel better mentally because you worked a little bit toward a goal." And like Tim, Paul has changed his diet for the better, usually opting for fish over red meat, for example. "Everything in moderation," he says. "And there are certain things to stay away from, too." While he acknowledges it can sometimes be challenging to forego certain foods, often he finds that it isn't. "I haven't eaten mayonnaise in like 20 years, now. I like mustard on everything, now, which I didn't before.... I like it better that way."

**Leading by Example**

The Daly brothers are committed to helping others learn that they, too, can change their lives for the healthier—and happier. They've been interviewed for National Public Radio,[1] and were featured in a segment of the HBO Documentary Series *The Weight of the Nation*.[2] But just as the story began with brothers, it remains for them about family. Explaining that his mother-in-law also has diabetes, he says he told his daughters, "heads up: this is what you got for genetics." "It's the same for my daughters," says Paul. "My wife has prediabetes [elevated blood glucose or insulin-resistance putting her at-risk for developing type 2 diabetes]; her father was diabetic; and my daughters see what I go through. So they're starting to adjust."

*And of the family friend who told him about the DPP Tim says, "Every time I see her, I thank her."*

Fortunately, for their families, Tim and Paul lead by example, looking out for each other, taking care of themselves, and making changes to lead longer, healthier lives. "We have to," Tim says reflectively. "You know, we want to enjoy our grandchildren, God willing." And of the family friend who told him about the study Tim says, "Every time I see her, I thank her."

[1] *http://www.npr.org/templates/story/story.php?storyId=122104219*

[2] *http://theweightofthenation.hbo.com/watch/main-films/Choices*